

REMARKS

Applicants would first like to state that the substitute specification filed February 19, 2002 contains no new matter. Further, Applicants submitted Response B on August 23, 2002 in reply to the April 23, 2002 Office Action ("Office Action") and Response C on October 7, 2002 in reply to an Advisory Action mailed on September 4, 2002 stating that Response B was not entered on the basis that several aspects of the amended claims created new issues. As such, Applicants have prepared the following amendments to the claims in response to those actions.

Claim Rejections - 35 USC § 112, para. 2

Claims 24 and 40 have been amended to remove the specific list of solvents, so the terms "such as," "and the like," and "including" are no longer present in these claims. In addition, claims 24 and 40 have been amended to distinguish the two solvents used in the crystallization steps as "a water-miscible first organic solvent" and "a second organic solvent having limited miscibility with water." The limitation "having limited miscibility with water" has support in the specification on p. 7, lines 11-12. Applicants note that the limitation "having limited miscibility or solubility with water" was objected to in the Office Action of October 24, 2001 for reasons of indefiniteness; Applicants, however, respectfully submit that such a limitation is readily understood by those skilled in the art for the reasons discussed below.

In light of the above amendments to claims 24 and 40, Applicants respectfully submit that these claims are no longer indefinite and as such are in condition for allowance.

For consistency, claims 36, 37, 44, and 44, which depend from claims 24 and 40, have been amended to refer to the organic solvent originally described as "having limited miscibility or solubility with water" as the "second organic solvent."

Also, claims 34-35 and 42-43 are hereby amended to describe a "water-miscible" organic solvent instead of a "water miscible or water-soluble" organic solvent, the terms being synonymous. These amendments make the claims consistent with claims 24 and 40, previously amended in like manner in Response A, from which claims 34-35 and claims 42 and 43 depend, respectively. Support for these amendments is found in the application, p. 7, lines 6-11.

The Applicants respectfully submit that the term "having limited miscibility with water" is not indefinite, because the common understanding for those skilled in the art is that the solubilities of organic solvents in water are defined by the terms miscible with water (infinitely soluble) and immiscible with water, (i.e. essentially no discernible or measurable amount of solubility). Organic solvents that cannot be categorized as either miscible or immiscible are understood to have limited miscibility with water. These terms are standard terms of art, and are thus not indefinite. For example, in Chapter 6 (Solutions and Colloids), section 4, (Solubility) of Bettelheim and March's General, Organic, and Biological Chemistry, Fifth Edition, (1998), Saunders College Publishing, it states "For solutions of liquids in liquids, [s]ome liquids are essentially insoluble in other liquids (gasoline in water) and others are soluble *to a limit* (emphasis added). For example, 100 g of water dissolves about 4 g of ethyl ether (another liquid)." (see p 181). Similarly, in Chapter 12 (Alcohols, Phenols, Ethers and Halides), section 7 (Physical Properties) it states ".... both alcohols and ethers are soluble in water, up to about three

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or four carbons. Alcohols and ethers of higher molecular weight, however, do not dissolve in water..." (see pp. 412-413).

Another standard textbook for organic chemistry, states "Methanol, ethanol, both propyl alcohols, and *tert*-butyl alcohol are completely miscible in water. The remaining butyl alcohols have solubilities in water between 8.3 and 26.0 g/100 mL. Pentane, by contrast, is virtually insoluble in water." (Solomon's Organic Chemistry, Sixth Edition, (1996), John Wiley & Sons, Inc.).

Using the terms miscible and immiscible to define the solubilities of organic solvents in water is a way of defining the limits by the two extremes. Those skilled in the art would be able to delineate between miscible and "immiscible" and understand that all other solvents are those with "limited miscibility." It is not necessary to list solvents, or limits of solubility, for those skilled in the art to understand these terms. As such, Applicant respectfully submits that such a limitation is not indefinite and that claims 24 and 40 are in condition for allowance.

In addition, new claims 48-51 have been added based on claims 24 and 40 submitted with the Preliminary Amendment of July 19, 2000. Support for the new claims is found in the specification on p. 2, line 29 through p. 3, line 7; p. 6, line 3 - through p. 7, line 37; and original claims 1 and 17. These new claims include a Markush group listing of solvents for the second organic solvent. Claims 48 and 50 list a Markush group of types of solvents; claims 49 and 51 list a Markush group of specific solvents. No new matter is added in these new claims.

In light of the above amendments, it is respectfully submitted that the bases for the § 112, para. 1 and 2 rejections have been removed. Applicants respectfully submit that all claims are thus in condition for allowance.

Claim Rejections - 35 USC § 102 (b)

Claims 40-42 and 46 remain rejected under 35 USC § 102(b) as being "clearly anticipated by US 4,319,039 [AB]." (See p.3, second paragraph.)

Applicants have amended claim 40 as suggested by the Examiner, replacing the open-ended phrase "comprise" with the close-ended phrase "consist of" in line 3 of claim 40.

In addition, Applicants re-emphasize that the presently claimed invention, with two combined crystallization steps, one involving the use of a water-miscible first solvent and the other the use of a second organic solvent having limited miscibility with water, as final steps to obtain HMG-CoA reductase inhibitors having a purity higher than 99.6%, is not anticipated by US 4,319,039, Albers-Schonberg et al. The Office Action states that the '039 patent discloses crystallization of the inhibitor from first "a mixture of chloroform/methanol/NH₄OH/ether (water immiscible) ... followed by crystallization from ethanol." See Office Action, p. 4. However, the '039 patent's protocol has two alternative pathways for purification of the HMG-CoA reductase inhibitors. The first involves recrystallization of the crude ammonium salt from the chloroform mixture (limited miscibility solvent) (see col. 13, lines 22-28) followed by a final purification from hot isopropanol with 5% concentrated ammonium hydroxide (a second limited miscibility solvent) (see col. 13, lines 61-68).

The alternative purification pathway involves converting the crude ammonium salt to the lactone form using toluene under reflux conditions, (limited miscibility solvent) (see col. 13, lines 29-37), recrystallizing the lactone from ethanol (water miscible solvent) (see col. 13, lines 43-45) and then converting the lactone back to the ammonium salt by 1) dissolving the lactone in basic methanol and filtering; 2) evaporating the methanol; 3) redissolving in acidic ethyl acetate; and 4) precipitating with a mixture of chloroform/methanol/concentrated NH_4OH followed with acetone (second limited miscibility solvent) (see col. 13, lines 46-59). The resulting crude ammonium salt product is subjected to final purification by crystallization from hot isopropanol with 5% concentrated ammonium hydroxide (third limited miscibility solvent) (see col. 13, lines 61-68).

Thus, the '039 patent does not disclose combined crystallization steps consisting of only two crystallization steps wherein one involves an organic solvent having limited miscibility with water, and the other involves a water-miscible organic solvent, as required by amended claims 40-46 in the present application.

In addition, the presently claimed invention results in HMG-CoA reductase inhibitors with greater than 99.6 % purity while maintaining high overall yields (see examples 1, 2, 4 and 5). In contrast, the '039 patent discloses a purification scheme that results in greater than or equal to 99 % purity for the lactone (see col. 13, lines 43-45) which is further purified to the ammonium salt form at greater than or equal to 99.5 % purity (see col. 14, lines 1-4). However, there are no results, in fact, evidencing successful purification as high as 99.6 % purity or greater, with concomitant high yields.

Applicants respectfully submit that such high purity, while maintaining high yields, is very difficult to achieve, because of undesired side products having similar structures to the desired inhibitor co-purifying with the desired inhibitor. Therefore, conventional purification schemes such as disclosed in the '039 patent may lead to high purity, but at purities greater than 99.6 % (if attained at all by such methods) the loss in yield is significant.

In summary, Applicants respectfully submit that the '039 patent does not anticipate the presently claimed invention as amended.

CONCLUSION

Claim 47 has been cancelled, and claims 24, 34-37, 40, and 42-45 have been amended. Specifically, in claims 24 and 40, and dependent claims 36, 37, 44, and 45, the two organic solvents disclosed in the two crystallization steps have been distinguished by the terms "water miscible first organic solvent" and "second organic solvent having limited miscibility with water," for which there is support in the specifications on p. 7, lines 11-12. In addition, the phrase "wherein the limited solubility is in the range of about 0.25 g/ 100 mL and about 30 g/ 100 mL," has been deleted from claim 40 because it was inadvertently and erroneously added in Response A.

With respect to the Office Action, Applicants respectfully submit that claim 40 as amended contains no new matter and is not indefinite. And with respect to the Advisory Action, Applicants respectfully submit that no new issues for review have been raised by the Markush list of solvents included in new claims 48-51, and no new issues for review have been raised with amended dependent claims 36-37 and 44-45, which now refer to "a second organic solvent."

Also, Applicants respectfully submit that claim 40, as amended to clarify the scope of the combined crystallization steps, (i.e. the steps "consist of" rather than "comprise") is not anticipated by the '039 patent.

For the reasons set forth above, it is submitted that all pending claims are in condition for allowance. Reconsideration of the claims and a notice of allowance are therefore requested.

Applicants petition for a three-month extension of time, and ask that any extension fee (to the extent not already paid), the fee for additional claims, and the

required fee for a Request for Continued Examination, be charged to deposit account number 19-472. If any additional fees are required for the timely consideration of this application, please charge deposit account number 19-4972. The Examiner is requested to telephone the undersigned if any matters remain outstanding so that they may be resolved expeditiously.

Date: October 23, 2002

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Timothy M. Murphy', with a long horizontal stroke extending to the right.

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Version with Markings to Show Changes

24. (twice amended) A process for the isolation and purification of HMG-CoA reductase inhibitors from mycelium biomass which comprises:

clarifying a mycelium broth and concentrating the clarified broth to a lower volume,

acidifying [æf] the concentrate to a pH value in the range of 4.5 to 7.5, followed by extracting the HMG-CoA reductase inhibitor with ethyl acetate;

optionally performing lactonization;

crystallizing the HMG-CoA reductase inhibitor from:

i) a water miscible first organic solvent; and

ii) [aa] a second organic solvent having limited miscibility with water[-
~~wherein before crystallization, the inhibitor is dissolved in said organic solvents at a~~
~~temperature of between about 10 to 40°C~~].

34. (once amended) The process according to claim 24, wherein the water-miscible [or water-soluble] first organic solvent used in the crystallization step is acetone or a low alkyl alcohol.

35. (once amended) The process according to claim 24, wherein the crystallization step from a water-miscible [or water-soluble] first organic solvent comprises dissolving the HMG-CoA reductase inhibitor in acetone, and then adding water thereto.

36. (twice amended) The process according to claim 24, wherein the crystallization step from ~~[an]~~ a second organic solvent comprises dissolving the HMG-CoA reductase inhibitor in said organic solvent at a concentration of 10 to 35 g/L, and removing one-third to three-fourth of said organic solvent.
37. (twice amended) The process according to claim 24, wherein the second organic solvent used in the crystallization step is ethyl acetate.
40. (twice amended) A process for the purification of HMG-CoA reductase inhibitors which comprises subjecting the HMG-CoA reductase inhibitor to combined crystallization steps, which ~~[comprise]~~ consist of crystallization from a water-miscible first organic solvent and crystallization from ~~[an]~~ a second organic solvent selected from the group consisting of butanol, isobutanol, amyl alcohol, hexanol, 2-ethylhexanol, benzyl alcohol, cyclohexanol, methylbutyl ketone, methyl isobutyl ketone, cyclohexanone, methyl acetate, ethyl acetate, n-propyl and isopropyl acetate, t-butyl, isobutyl, sec-butyl acetate, amyl acetate, diethyl ether, diisopropyl ether, methylene chloride, chloroform, acetonitrile, and mixtures of these solvents, [wherein the limited solubility is in the range of about 0.25 g/100 mL and about 30 g/100 mL,] as final steps to obtain HMG-CoA reductase inhibitors having a purity higher than 99.6%.
42. (once amended) The process according to claim 40, wherein acetone or a low alkyl alcohol is used as the water-miscible ~~[or water soluble]~~ organic solvent.

43. (once amended) The process according to claim 40, wherein the crystallization from a water-miscible [~~or water-soluble~~] organic solvent comprises dissolving the HMG-CoA reductase inhibitor in acetone, and then adding water thereto.

44. (twice amended) The process according to claim 40, wherein said crystallization from ~~an~~ a second organic solvent comprises dissolving the HMG-CoA reductase inhibitor in said organic solvent at a concentration of 10 to 35 g/L, and removing one-third to three-fourth of said organic solvent.

45. (twice amended) The process according to claim 40, wherein ethyl acetate is used as the second organic solvent.

48. (new) A process for the isolation and purification of HMG-CoA reductase inhibitors from mycelium biomass which comprises:

clarifying a mycelium broth and concentrating the clarified broth to a lower volume,

acidifying the concentrate to a pH value in the range of 4.5 to 7.5, followed by extracting the HMG-CoA reductase inhibitor with ethyl acetate;

optionally performing lactonization;

crystallizing the HMG-CoA reductase inhibitor from:

i) a water miscible first organic solvent; and

ii) a second organic solvent selected from the group consisting of higher alkyl alcohols, higher alkyl ketones, esters, ethers, chlorinated hydrocarbons, acetonitrile, and mixtures of these solvents.

49. (new) A process for the isolation and purification of HMG-CoA reductase inhibitors from mycelium biomass which comprises:

clarifying a mycelium broth and concentrating the clarified broth to a lower volume,

acidifying the concentrate to a pH value in the range of 4.5 to 7.5, followed by extracting the HMG-CoA reductase inhibitor with ethyl acetate;

optionally performing lactonization;

crystallizing the HMG-CoA reductase inhibitor from:

i) a water miscible first organic solvent; and

ii) a second organic solvent selected from the group consisting of butanol, isobutanol, amyl alcohol, hexanol, 2-ethylhexanol, benzyl alcohol, cyclohexanol, methylbutyl ketone, methyl isobutyl ketone, cyclohexanone, methyl acetate, ethyl acetate, n-propyl, isopropyl acetate, t-butyl, isobutyl, sec-butyl acetate, amyl acetate, diethyl ether, diisopropyl ether, methylene chloride, chloroform, acetonitrile, and mixtures of these solvents.

50. (new) A process for the purification of HMG-CoA reductase inhibitors which comprises subjecting the HMG-CoA reductase inhibitor to combined crystallization steps, which consist of crystallization from a water-miscible first organic solvent and

crystallization from a second organic solvent selected from the group consisting of higher alkyl alcohols, higher alkyl ketones, esters, ethers, chlorinated hydrocarbons, acetonitrile, and mixtures of these solvents, as final steps to obtain HMG-CoA reductase inhibitors having a purity higher than 99.6%.

51. (new) A process for the purification of HMG-CoA reductase inhibitors which comprises subjecting the HMG-CoA reductase inhibitor to combined crystallization steps, which consist of crystallization from a water-miscible first organic solvent and crystallization from a second organic solvent selected from the group consisting of butanol, isobutanol, amyl alcohol, hexanol, 2-ethylhexanol, benzyl alcohol, cyclohexanol, methylbutyl ketone, methyl isobutyl ketone, cyclohexanone, methyl acetate, ethyl acetate, n-propyl and isopropyl acetate, t-butyl, isobutyl, sec-butyl acetate, amyl acetate, diethyl ether, diisopropyl ether, methylene chloride, chloroform, acetonitrile, and mixtures of these solvents, as final steps to obtain HMG-CoA reductase inhibitors having a purity higher than 99.6%.

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